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February 18, 2005

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
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Re: Docket No. 2004N–0081
Use of Materials Derived from Cattle in Human Food and Cosmetics: Interim Final Rule (69 Fed. Reg. 42256; July 14, 2004)

To Whom It May Concern:

This letter is submitted to the above-referenced docket by the Gelatin Manufacturers of Europe (GME). GME represents the nine largest European manufacturers that account for 96 percent of European gelatin production and approximately 45 percent of worldwide gelatin production.

On October 20, 2003, GME and the Gelatin Manufacturers Institute of America (GMIA) submitted a Citizen petition requesting modification of the "Guidance for Industry: The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by BSE in FDA-Regulated Products for Human Use" (Docket No. 97D-0411, September 1997) ("gelatin guidance").

On October 12, 2004, GME submitted comments to the above-referenced docket with respect to the interim final rule on the use of materials derived from cattle in human food and cosmetics. In its comments, GME explained that gelatin made from bovine raw materials is safe because (1) the manufacturing processes used to make gelatin have been validated to inactivate BSE infectivity, and (2) only safe raw materials are used.

Since our comments were submitted, GME has become aware that FDA may need additional information on topics related to the interim final rule, including (1) how to verify that European gelatin is made using safe raw materials and using manufacturing processes that have been validated to inactivate BSE infectivity, (2) what restrictions are in place on the use of imported gelatin in animal feed, (3) the significance of the degree of infectivity reduction in the GME studies, and (4) the need to amend FDA's gelatin guidance. Accordingly, we have prepared a brief summary of this additional information in this letter.

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We request that FDA reopen the comment period for the interim final rule for purposes of receiving this additional information. The issues raised by the interim final rule are complex and should be analyzed with the benefit of all necessary information, including new information that may be submitted to the agency as a result of evolving understanding of governmental policy and evolving science. The information in this letter is important to assisting FDA in understanding how its policies may be affected by controls on gelatin safety that are in place in Europe, and other issues. The acceptance of this new information by the agency will not have an adverse effect on the implementation of the interim final rule because that rule is already effective. For these reasons, GME believes it would be consistent with the Administrative Procedure Act and FDA regulations to reopen the comment period for purposes of receiving this information.

(1) ***Additional information on how to verify that European gelatin is made using safe raw materials and using manufacturing processes that have been validated to inactivate BSE infectivity***

In Europe, the use of safe raw materials and gelatin manufacturing processes that have been validated to inactivate BSE infectivity is mandatory under European Commission decisions 1999/724/EC and 2002/1774/EC. In particular, decision 1999/724/EC requires that relevant ruminant bone material must be subjected to a process which ensures that all bone material is finely crushed and degreased with hot water and treated with dilute hydrochloric acid (at minimum concentration of 4% and pH < 1.5) over a period of at least two days, followed by an alkaline treatment of saturated lime solution (pH > 12.5) for a period of at least 20 days, with a sterilization step of 138-140°C during four seconds or by an equivalent process approved by the Commission. In addition, the official national registration number of a plant confirms compliance with these regulations.

FDA also has taken steps to assure that European manufacturers are operating consistently with these requirements. In 2003, FDA inspected the principal producers in Europe, and further inspections may be conducted at any time.

European producers themselves have also reviewed their practices to assure compliance with these requirements. For example, all bovine gelatin-producing plants have received a certificate from SGS (Société Générale de Surveillance, a Swiss independent surveyor) confirming compliance of their industrial processes with the design used in GME's inactivation studies. The SGS validation was performed taking into account typical production conditions found throughout Europe.

As a result, all batches of bovine gelatin produced in Europe are made using safe raw materials with manufacturing processes that have been validated to inactivate BSE infectivity. If necessary, it is possible to obtain an official health certificate attesting to this fact (and some

countries do require such certificates). If FDA were to require additional assurance of the safety of raw materials and manufacturing processes used for imports of gelatin, this could be provided by European manufacturers in the form of health certificates. This requirement could be implemented under the import permit system maintained by USDA's Animal and Plant Health Inspection Service (APHIS).

(2) ***Additional information on restrictions on the use of imported gelatin in animal feed***

In the United States, regulatory requirements are already in place to assure that imported gelatin is not inappropriately used in animal feed. Imports of gelatin from BSE countries are regulated by APHIS under 9 CFR 94.18. That regulation prohibits the importation of gelatin unless the gelatin is "imported for use in human food, human pharmaceutical products, photography, or some other use that will not result in the gelatin coming in contact with ruminants in the United States." 9 CFR 94.18(c)(1). This requirement is implemented by European manufacturers by means of written verification by customers to confirm that gelatin will be used in a manner consistent with the regulation.

(3) ***Additional information on the significance of infectivity reduction in the studies conducted by GME***

The following is a summary of the extent to which infectivity was inactivated in the GME studies (complete information was provided with our comments of October 12, 2004):

- **Complete Limed Bone Gelatin Process (Tested with mice 301V BSE strain):** Infectivity reduced more than $10^{4.9}$ ID_{50}, the maximum that could be measured in the study. The actual infectivity reduction may have been greater.

- **Limed Bone Gelatin Process until Extraction (Tested with hamster 263K Scrapie strain):** Infectivity reduced more than $10^{4.6}$ ID_{50}. The effect of purification of the gelatin extract (i.e., filtration, ion-exchange and UHT-sterilization) was not tested in this study, so the total reduction contributed by the entire manufacturing process would likely be greater.

- **Complete Acid Bone Gelatin Process (Tested with mice 301V BSE strain):** Infectivity reduced more than $10^{4.8}$ ID_{50}, the maximum that could be measured in the study. The actual infectivity reduction may have been greater.

- **Acid Bone Gelatin Process with NaOH Pre-treatment until Purification (Tested with mice 301V BSE strain):** Infectivity reduced more than $10^{5.4}$ ID_{50}, the maximum that could be measured in the study. The effect of purification of the gelatin extract (i.e., filtration, ion-exchange and UHT-sterilization) was not tested in this study, so the total reduction contributed by the entire manufacturing process would likely be greater.

As we noted in our October 12, 2004 comments, these data were thoroughly reviewed by FDA's TSE Advisory Committee, which concluded that they "demonstrate a reduction in infectivity that is sufficient to protect human health,"[1] and by the Scientific Steering Committee of the European Union, which concluded that the manufacturing process is "considered to be sufficient for the production of safe gelatine."[2] Accordingly, by any measure, the levels of infectivity reduction demonstrated in the GME studies are sufficient to assure safety.

(4) ***Additional information on the need to amend FDA's gelatin guidance***

In our October 12, 2004 comments, we discussed FDA's September 1997 gelatin guidance. This guidance is inconsistent with the interim final rule,[3] and it appears still to be in place for FDA-regulated products other than foods and cosmetics. As a result, the guidance establishes inconsistent standards for gelatin capsules, which may be used in both foods (dietary supplements) and pharmaceuticals.

As discussed in section 1 above, FDA can if it wishes take steps to verify that imported gelatin is made using safe raw materials and using manufacturing processes that have been validated to inactivate BSE infectivity. Therefore, there is no need for different, inconsistent standards to be present in the gelatin guidance. This guidance should be either (1) eliminated and replaced by the interim final rule (as amended by our comments of October 12, 2004), or (2) harmonized with the interim final rule and amended in accordance with our Citizen Petition of October 20, 2003.

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[1] Transcript of TSEAC meeting, July 17, 2003, pp. 150, 158. The vote was 7 in favor, 1 abstain, and 1 against.

[2] Updated Opinion on the Safety with Regard to TSE Risks of Gelatine derived from Ruminant Bones or Hides, adopted by the Scientific Steering Committee at its Meeting of 6-7 March 2003 (http://europa.eu.int/comm/food/fs/sc/ssc/out321_en.pdf).

[3] Our Citizen Petition of October 20, 2003 set forth why the Guidance cannot be literally complied with by EU gelatin manufacturers. The Petition explained that the Guidance's requirement that heads, spines, and spinal cords be removed at the slaughterhouse "directly after slaughter" and "as the first procedure following slaughter" must be revised to permit these materials to be removed at any time or place after slaughter. The Petition also explained that the Guidance's requirement that cattle come from "BSE-free herds" must be revised to refer to standards that are in place to evaluate BSE risk in different geographic areas.

Thank you for considering the additional information provided by these comments.

Respectfully submitted,

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Counsel to the Gelatin Manufacturers of Europe

cc: Rebecca Buckner, Ph.D. (HFS-306)
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